

Effect of nitrate treatment on functional capacity and exercise time in patients with heart failure: a systematic review and meta-analysis

Wenjie Long^{1,2,*}, Huili Liao^{1,*}, Qingqing Liu³,
Yile Ning³, Tingchun Wu^{3,4}, Jinhua Kang³,
Jianhong Liu¹, Shaoxiang Xian^{1,2} and
Zhongqi Yang^{1,2} 

Abstract

Objectives: Heart failure (HF) is a common and potentially fatal condition. In 2015, HF affected approximately 40 million people globally. Evidence showing that the use of nitrates can improve clinical outcomes in patients with HF is limited. This study aimed to assess the effect of nitrates on functional capacity and exercise time in patients with HF.

Methods: PubMed, Cochrane Library, and Embase databases were reviewed for articles on the use of nitrates and other treatments for patients with HF. The primary endpoints were the 6-minute walk test distance, exercise time, and quality of life. Secondary endpoints were all-cause mortality, arrhythmia, hospitalization, and worsening HF. The weighted mean difference, risk ratio, and 95% confidence interval were calculated.

Results: A total of 14 related studies that comprised 26,321 patients were included. No significant differences were found in the 6-minute walk test distance, exercise time, and quality of life between

¹Department of Geriatrics, The First Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China

²Lingnan Medical Research Center, Guangzhou University of Chinese Medicine, Guangzhou, China

³The First Clinical Medical College, Guangzhou University of Chinese Medicine, Guangzhou, China

⁴Department of Cardiology, The Second Affiliated Hospital of Guizhou University of Traditional Chinese Medicine, Guiyang, China

*These authors contributed equally to this work.

Corresponding author:

Zhongqi Yang, Department of Geriatrics, The First Affiliated Hospital of Guangzhou University of Chinese Medicine, No. 12 Jichang Road, Baiyun District, Guangzhou, 510405, P.R. China.
Email: yang_zhongqi@163.com



the nitrate and control treatment groups. There were also no differences in all-cause mortality, the incidence of arrhythmia, hospitalization, and worsening HF between these two groups.

Conclusion: Patients with HF who receive nitrate treatment do not have better quality of life or exercise capacity compared with controls.

Keywords

Heart failure, meta-analysis, nitrate, 6-minute walk test, exercise, quality of life

Date received: 18 November 2019; accepted: 15 June 2020

Introduction

Cardiovascular disease (CVD) is the main cause of morbidity and mortality worldwide.^{1,2} CVD is associated with a decline in quality of life and an increase in disability, greatly increasing the cost of medical treatment.^{3,4} Heart failure (HF) is one of the most common CVDs in the world. HF continues to be a huge burden on patients, care givers, and health care systems. In Europe, approximately 6.5 million people are currently living with CVD,⁵ with a prevalence of $\geq 10\%$ among patients aged 70 years and older.⁶ HF is the endpoint of all CVDs.⁷ The number of patients with HF has increased rapidly in most industrialized countries because of an increase in survival after acute myocardial infarction and aging of the population.⁶ HF is an important cause of death in the UK, where approximately 5% of people die from HF,⁵ and only 25% of patients survive beyond 5 years after their first admission.⁸

Organic nitrates are often used to treat HF.^{9–11} Short-term studies have shown that nitrate-induced venodilation significantly reduces right and left ventricular filling pressures, while arterial dilation is less obvious. Heart rate remains stable, while cardiac output usually slightly increases.^{12–14} Hemodynamic effects of nitrates might reduce pulmonary congestion and improve exercise ability of patients with preserved ejection fraction.¹⁵ Inadequate improvement in

exercise endurance and its adverse effect on daily activity levels may be associated with the pathophysiology of HF with preserved ejection fraction. Vascular stiffness and ventricular contraction, chronotropic incompetence, autonomic nerve dysfunction, and changes in baroreflex sensitivity are usual and may restrict hemodynamic improvement of nitrates.^{16,17} Hydralazine and nitrate may work together in patients with congestive HF.¹⁸ While nitrate therapy appears to be beneficial for HF,^{19,20} hydralazine is also an effective vasodilator with some antioxidant effects that help prevent non-degradation.²¹ Although the exact cardiovascular properties of hydralazine are not fully understood, it directly reduces peripheral vascular resistance by relaxing vascular smooth muscle cells.²² Hydralazine might also inhibit activation of a membrane-related oxidase responsible for increasing production of superoxide, which causes nitrate tolerance.²³

Several studies have compared nitrates with control treatments for HF, but no consistent outcomes have been reported.^{24–36} Therefore, this meta-analysis was conducted to assess the efficacy and safety of nitrates compared with control treatment for HF.

Material and methods

The present meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis

guidelines³⁷ and by following the published research protocol on PROSPERO (CRD: 42017069882). Ethics approval of the study protocol was not required because the study was a meta-analysis.

The following terms and their combinations were used to search PubMed, Embase, and Cochrane library databases for relevant studies up to September 2019: “nitrate/nitrates” and “heart failure.” All scanned citations, abstracts, and studies were reviewed. Additionally, references to retrieved manuscripts were cross-searched manually for further relevant publications.

The criteria for inclusion were as follows: (1) studies that involved patients with HF (regardless of ejection fraction or phenotype); (2) studies that had at least two groups, with one group receiving treatment with nitrates and another group receiving treatment without nitrates; and (3) studies that provided risk ratios (RRs) with 95% confidence intervals (CIs) or the ability to calculate these statistics from the data provided. The criteria for exclusion were as follows: (1) studies that used an overlapping database or the same population; and (2) studies that used cell or animal models.

All available data were extracted independently by two researchers on the basis of above-mentioned inclusion criteria. Subsequently, any differences were resolved through discussions with a third author. The following data were extracted from each study: first author’s name, year of publication, research design, country, sex, mean age, sample size, follow-up time, and outcomes assessed. The primary endpoints were the 6-minute walk test distance, exercise time, and quality of life. The secondary endpoints were all-cause mortality, arrhythmia, hospitalization, and worsening HF. The Cochrane Collaboration’s risk-of-bias tool was used to evaluate the quality of randomized, controlled trials (RCTs) for assessment of bias risk.³⁸ The Newcastle–Ottawa 9-star system was used to assess

the quality of cohort studies. A high-quality study was defined as a study with more than seven stars.³⁹

The weighted mean difference (WMD) and 95% CI were calculated for continuous data, and the RR and 95% CI were calculated for binary data. Data were combined according to the random-effects (DerSimonian and Laird’s method) or fixed-effects model depending on the chi-square-based Q test and I^2 statistic. A P value < 0.05 was considered statistically significant. If heterogeneity was significant, the random-effects model was adopted. Otherwise, a fixed-effects model was adopted. By removing one study for sensitivity analysis, the relative effect of each study on comprehensive assessment was evaluated. Publication bias was assessed by visual inspection of Begg’s funnel plot symmetry and evaluation of Egger’s test ($P < 0.05$). Statistical analysis was performed using Stata software version 12.0 (Stata Corp, College Station, TX, USA) and all tests were double sided.

Results

Studies and outcomes

A total of 138 studies were related to the search terms and 92 unrelated studies were subsequently excluded. The remaining studies were systematically evaluated and 29 studies were full text. After reading the full text, 15 studies were considered inappropriate and excluded, and the remaining 14 studies were qualitatively analyzed. Finally, this meta-analysis included 14 articles, which involved 26,321 patients. The study selection process is shown in Figure 1. All studies were clinical studies, including nine RCTs and four cohort studies. The 14 studies represented 7647 and 18,674 patients with HF in the nitrate group and the control treatment group, respectively. The follow-up interval of

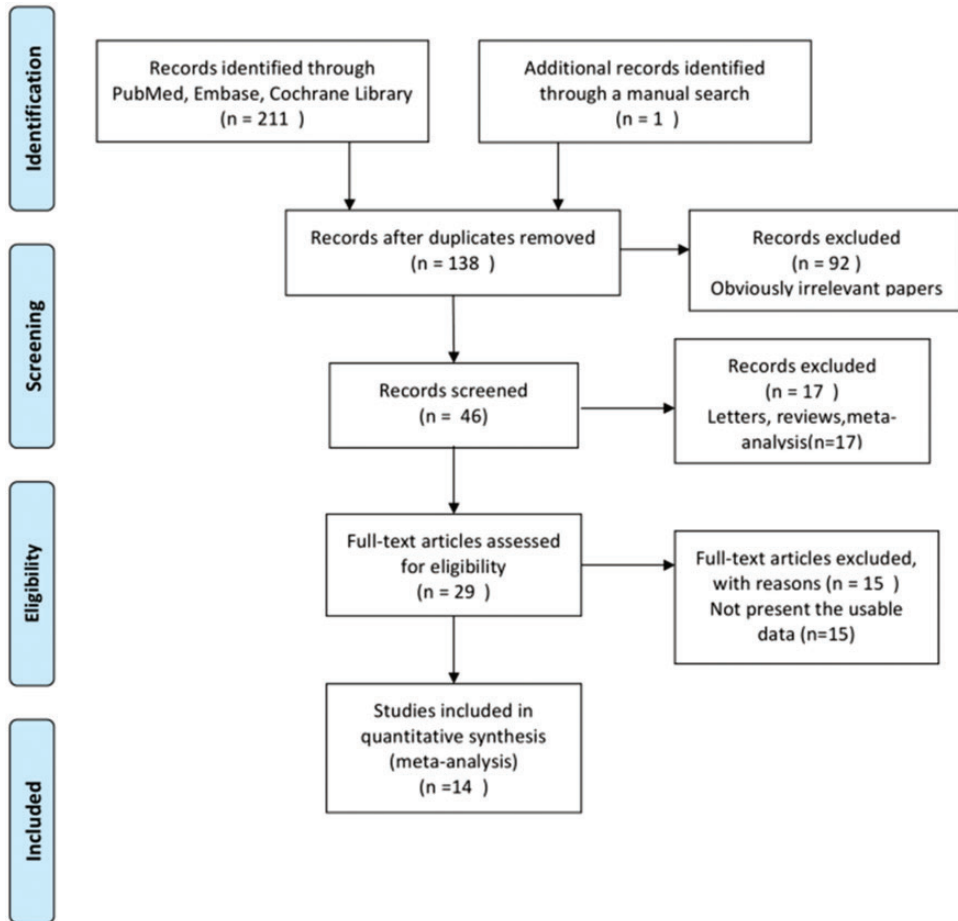


Figure 1. Flow diagram of identification of studies.

these studies ranged from 1 to 57 months. A summary of biases determined in each RCT is shown in Figure 2. All of the included studies were of medium or high quality. The main features of the qualified studies are shown in Table 1. Table 2 lists the methodological quality of cohort studies based on the Newcastle–Ottawa Scale. The quality of the cohort studies was generally high; two studies had eight stars and two studies had seven stars.

Two studies^{32,34} provided outcomes regarding the 6-minute walk test distance in patients who received nitrates and control treatments. No heterogeneity was found

among the two studies. Therefore, a fixed-effects model was used. The 6-minute walk test distance was not significantly different between patients who received nitrates and those who received control treatment (WMD = 2.04, 95% CI: -16.90–20.99, $P_{\text{heterogeneity}} = 0.795$, $I^2 = 0\%$) (Figure 3a).

Two studies^{27,28} provided outcomes regarding the exercise time in patients who received nitrates and control treatments, and were included in the meta-analysis. Significant heterogeneity was found among the two studies. Therefore, a random-effects model was used. No significant difference was observed in the exercise time between patients

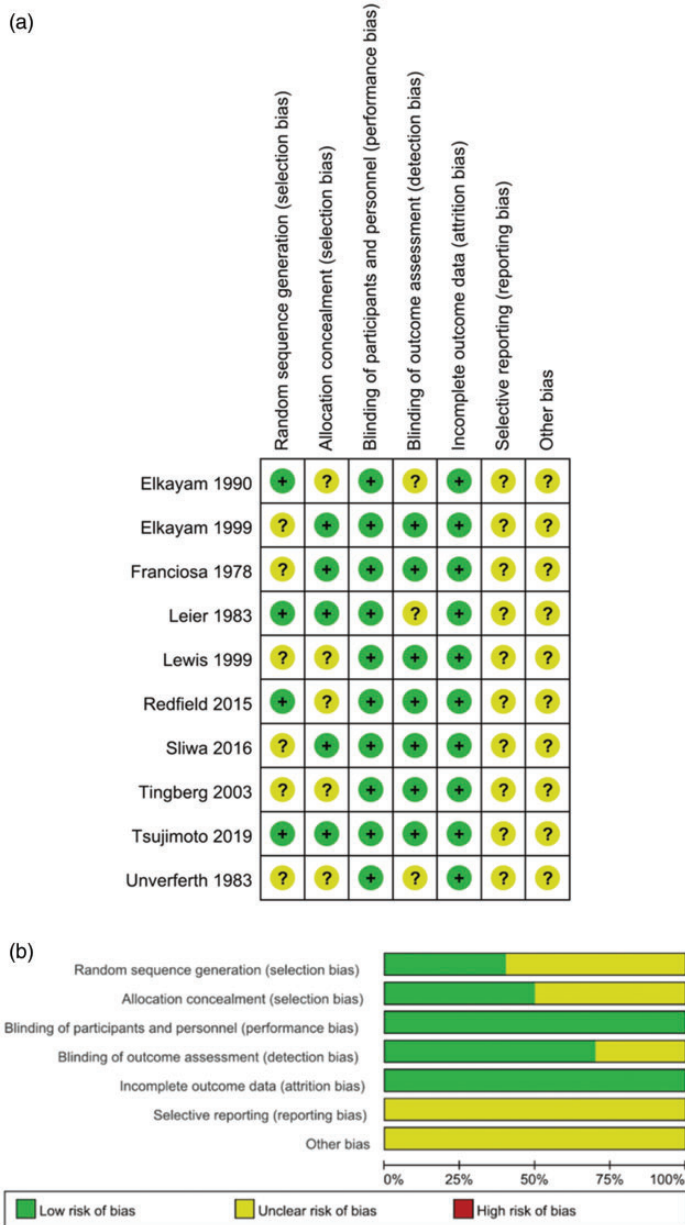


Figure 2. Risk of bias assessments for randomized trials included in the meta-analysis. (a) Risk of bias summary; and (b) risk of bias graph. (+): Low risk of bias; (?): unclear risk of bias; and (-): high risk of bias.

who received nitrates and those who received control treatment (WMD = 59.17, 95% CI: -27.34–145.68, $P_{\text{heterogeneity}} = 0.013$, $I^2 = 83.9\%$) (Figure 3b).

Two studies^{28,32} provided outcomes regarding quality of life in patients who received nitrates and control treatments. No significant heterogeneity was found

Table 1. Characteristics of the studies included in this meta-analysis.

Author/year of publication	Country	Sex (male, %)	Mean age (years)	Phenotype	Intervention		Follow-up (months)	Study design	Outcomes assessed
					Nitrates	Control			
Franciosa/1978 ¹⁸	USA	93.7	55.3 ± 1.5	Congestive	ISDN 160 mg PO (N = 7)	Placebo (N = 7)	4	RCT	All-cause mortality, hospitalization, arrhythmia, worsening heart failure
Leier/1983 ¹⁹	USA	80	Nitrate: 51 ± 16 Control: 47 ± 15	Congestive	ISDN 160 mg PO (N = 13)	Placebo (N = 17)	3	RCT	All-cause mortality
Unverferth/1983 ²⁰	USA	75.5	57 ± 10	Congestive	ISDN 160 mg PO (N = 6)	Placebo (N = 11)	3	RCT	All-cause mortality
Elkayam/1990 ²¹	USA	89.3	55 ± 10	Congestive	ISDN 160 mg PO (N = 20)	Nifedipine 80 mg PO (N = 21)	6.5	RCT	Treadmill exercise time
Lewis/1999 ²³	Israel	94.1	57 ± 8	Congestive	IS-5-MIN 50 mg PO (N = 67)	Placebo (N = 69)	6	RCT	All-cause mortality, arrhythmia, worsening heart failure
Elkayam/1999 ²²	USA	82.7	Nitrate: 48 ± 3 Control: 48 ± 4	HF/rEF	NTG 57 ± 5 mg transdermal patch OD (N = 14)	Placebo (N = 15)	3	RCT	All-cause mortality, hospitalization, quality of life, treadmill exercise time
Tingberg/2003 ²⁴	Sweden	75	Nitrate: 63 ± 10 Control: 65 ± 9	HF/rEF	ISMN 60 mg PO (N = 47)	Placebo (N = 45)	12	RCT	All-cause mortality, hospitalization, worsening heart failure
Herrero-Puente/2015 ²⁵	Spain	43.4	Nitrate: 78.6 ± 10.2 Control: 79.8 ± 9.9	Acute	NTG 50 mg IV (N = 796)	Placebo (N = 2382)	1	Cohort	All-cause mortality
Redfield/2015 ²⁶	USA	42.7	Nitrate: 69 ± 9 Control: 69 ± 10	HF/rEF	ISMN 30-120 mg PO (N = 51)	Placebo (N = 59)	1.5	RCT	Arrhythmia, worsening heart failure, 6-minute walk test distance, quality of life
Ho/2016 ²⁷	Canada	51.7	77	Acute	NTG (N = 3153)	No nitrates (N = 7925)	12	Cohort	All-cause mortality, hospitalization
Sliwa/2016 ²⁸	South Africa	59.9	Nitrate: 56.7 ± 12.7 Control: 56.9 ± 13.3	Acute	Hydralazine 50 mg/ISDN 20 mg IV (N = 518)	Placebo (N = 532)	6	RCT	6-minute walk test distance
Lim/2017 ²⁹	Sweden	51.9	Nitrate: 79 ± 9 Control: 79 ± 8	HF/rEF	ISDN/ISMN (N = 2235)	No nitrates (N = 4470)	25	Cohort	All-cause mortality

(continued)

Table 1. Continued.

Author/year of publication	Country	Sex (male, %)	Mean age (years)	Phenotype	Intervention		Follow-up (months)	Study design	Outcomes assessed
					Nitrates	Control			
Ural/2017 ³⁰	Turkey	68.9	65.1 ± 11.6	HFrEF	ISDN/ISMN 20–60 mg PO (N = 212)	No nitrates (N = 212)	56	Cohort	All-cause mortality, hospitalization
Tsujimoto/2019 ⁴⁶	Japan	48.4	Nitrate: 69.6 ± 9.2 Control: 68.4 ± 9.6	HFrEF	Nitrates (N = 508)	No nitrates (N = 2909)	57	RCT	Hospitalization

ISDN: isosorbide dinitrate; NTG: nitroglycerin; ISMN: isosorbide mononitrate; IS-5-MN: isosorbide-5-mononitrate; RCT: randomized, controlled trial; HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; IV: intravenously; PO: per os (orally); OD: once a day.

Table 2. Methodological quality of cohort studies included in the meta-analysis.*

First author/year	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcome of interest present at the start of the study	Control for important factor or additional factor	Outcome assessment	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total quality scores
Herrero-Puente/2015	☆	☆	☆	☆	☆	☆	☆	☆	8
Ho/2016	☆	☆	☆	☆	☆	☆	☆	☆	8
Lim/2017	☆	☆	☆	—	☆	☆	☆	☆	7
Ural/2017	☆	☆	☆	—	☆	☆	☆	☆	7

*A study could be awarded a maximum of one star for each item, except for the item “control for important factor or additional factor”.

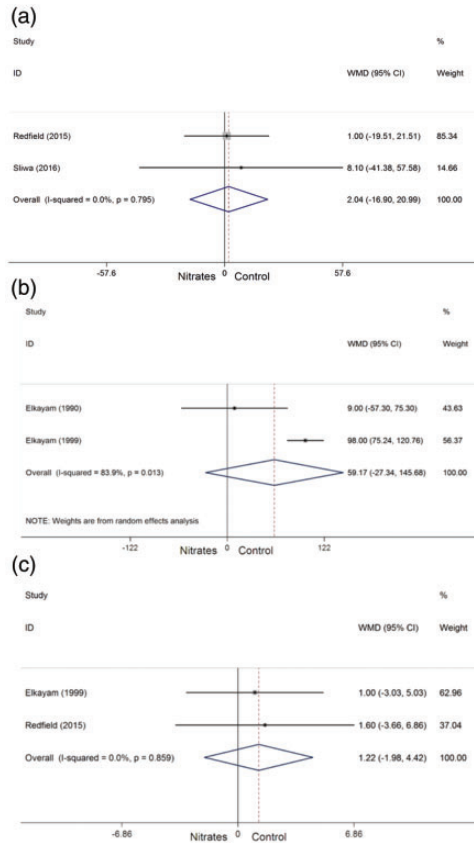


Figure 3. Forest plots showing the effect of nitrates on primary outcomes in patients with heart failure. (a) Six-minute walk test distance; (b) exercise time; and (c) quality of life. WMD, weighted mean difference; CI, confidence interval.

among the two studies. Therefore, a fixed-effects model was used. Quality of life was not significantly different between patients who received nitrates and those who received control treatment (WMD = 1.22, 95% CI: -1.98–4.42, $P_{\text{heterogeneity}} = 0.859$, $I^2 = 0\%$) (Figure 3c).

All-cause mortality

A total of 14 studies were included in the meta-analysis of adverse events. All-cause mortality was reported in 10 studies,^{18–20,22–25,27,29,30} which all compared nitrate with control treatments. A low heterogeneity between studies was found.

Therefore, the fixed-effects model was used. The incidence of all-cause mortality was not significantly different between patients who received nitrates and those who received control treatment (RR = 1.03, 95% CI: 0.98–1.07, $P_{\text{heterogeneity}} = 0.186$, $I^2 = 28.1\%$) (Figure 4a).

Arrhythmia

Arrhythmia was reported in three studies.^{24,29,32} No significant heterogeneity between studies was found. Therefore, the fixed-effects model was used. The incidence of arrhythmia was not significantly different between patients who received nitrates

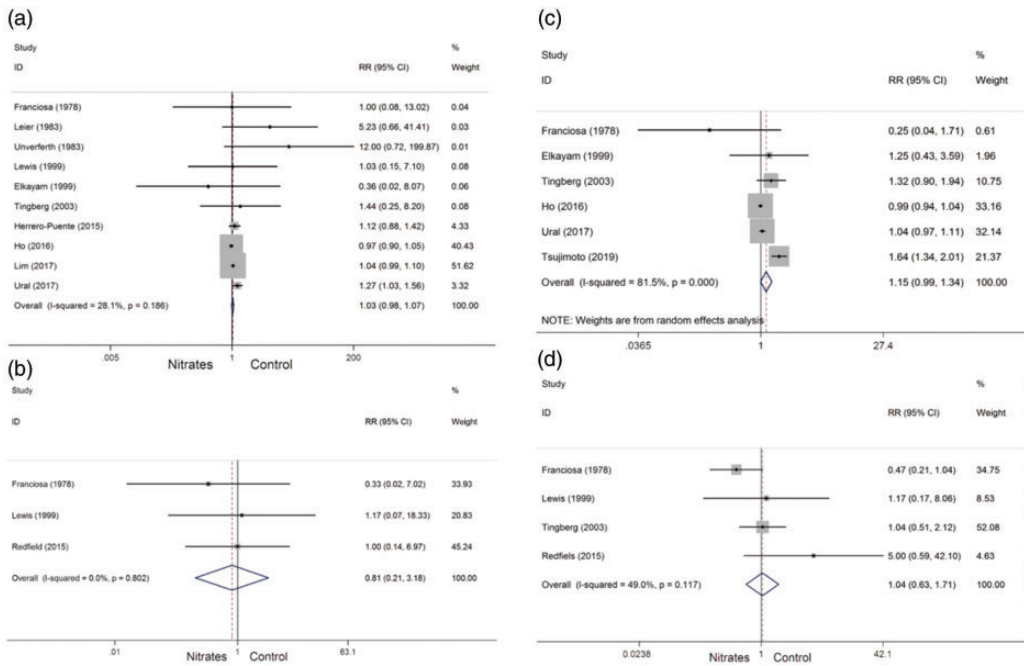


Figure 4. Pooled risk ratio of adverse events with nitrates in patients with heart failure. (a) All-cause mortality; (b) arrhythmia; (c) hospitalization; and (d) worsening heart failure. RR, risk ratio; CI, confidence interval.

and those who received control treatment (RR = 0.81, 95% CI: 0.21–3.18, $P_{\text{heterogeneity}} = 0.802$, $I^2 = 0\%$) (Figure 4b).

Hospitalization

Hospitalization was reported in six studies.^{24,28,30,33,36,40} A high heterogeneity between studies was found. Therefore, the random-effects model was used. The incidence of hospitalization was not significantly different between patients who received nitrates and those who received control treatment (RR = 1.15, 95% CI: 0.99–1.34, $P_{\text{heterogeneity}} < 0.001$, $I^2 = 81.5\%$) (Figure 4c).

Worsening HF

Worsening HF was reported in four studies.^{24,29,30,32} A low heterogeneity between studies was found. Therefore, the fixed-

effects model was used. However, the incidence of worsening HF was not significantly different between patients who received nitrates and those who received control treatment (RR = 1.04, 95% CI: 0.63–1.71, $P_{\text{heterogeneity}} = 0.117$, $I^2 = 49\%$) (Figure 4d).

Sensitivity analysis was used to evaluate the effect of a single data set on the summary results by deleting each eligible study in turn. As shown in Figure 5a, 5b, and 5c, when any single study was removed, the overall statistical significance remained the same, which indicated that the results were statistically robust.

Finally, some degree of asymmetry in funnel plots was observed. However, Begg’s and Egger’s tests showed no significant publication bias in all-cause mortality (Begg’s test: $P = 0.721$; Egger’s test: $P = 0.158$) (Figure 6).

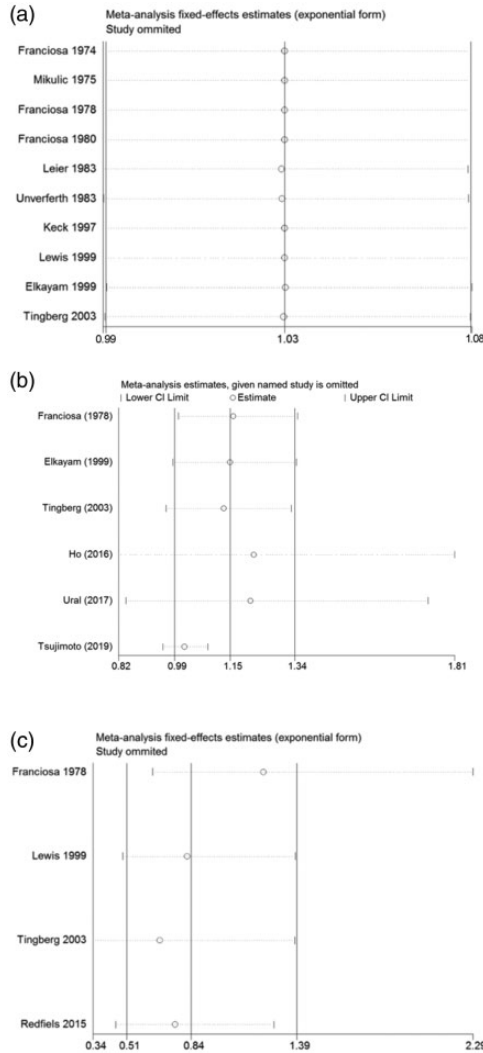


Figure 5. Sensitivity analysis examining the effect of individual studies on pooled results. (a) All-cause mortality; (b) hospitalization; and (c) worsening heart failure. CI, confidence interval.

Discussion

HF is a common and potentially fatal condition. Signs and symptoms of HF commonly include shortness of breath, excessive tiredness, and leg swelling.^{5,6} Patients suffer from exercise intolerance, which diminishes their ability to perform normal activities of daily living, and thus compromises their quality of life. Evidence

showing that use of nitrates in HF can improve clinical outcomes is limited.^{5,6,28} Some studies compared treatments with nitrate and without nitrate in patients with HF to examine the benefits of nitrates.^{35,36} This systematic review and meta-analysis compared the efficacy and safety of nitrates for patients with HF. We found no significant difference in the 6-minute walk test

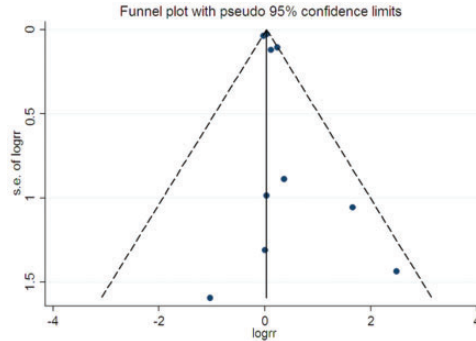


Figure 6. Funnel plot for a publication bias test of all-cause mortality. Each point represents a separate study for the indicated association. s.e., standard error; logrr, logarithmic risk ratio.

distance, exercise time, and quality of life between the nitrate and control treatment groups. Moreover, no significant differences were found in all-cause mortality, the incidence of arrhythmia, hospitalization, and worsening HF between these two groups.

A meta-analysis is a method used to obtain quantitative information-related evidence based on a complete set of studies.⁴¹ A typical systematic review uses a meta-analysis method to combine the effects of a specific interest estimate and obtain a summary estimation effect.⁴² The present meta-analysis, which comprised 26,321 patients with HF from 14 studies, is the most extensive study to investigate the safety and efficacy of nitrates to date. Recently, Farag et al.⁴³ conducted a systematic review of the efficacy and safety of nitrates in patients with HF. In the present meta-analysis, more eligible studies were identified and a detailed analysis was performed, whereas Farag et al.⁴³ only analyzed a single study by systematic review.

In our analysis, the quality of randomized and nonrandomized studies was assessed using the Cochrane Collaboration's risk-of-bias tool and the Newcastle–Ottawa scale, respectively. Using the Cochrane Collaboration's risk-of-bias tool, we found only a moderate degree of confidence in the results. This finding is attributed to an

unclear risk of selection bias observed among most of the included studies because of an unclear description of the exact randomization procedure and/or allocation concealment and also because of stratification during randomization. Begg's funnel plot and Egger's test were used to assess the publication bias of published studies in our study, and no publication bias was found.

According to the European Society of Cardiology Heart Failure Long-Term Registry,⁴⁴ 25% of patients with acute HF took nitrate orally before admission, and the use of prescription drugs increased to 32%. In patients with HF with reduced ejection fraction, the utilization rate of nitrate was 18%, while hydrazine was not used in combination with nitrate. Because 54% of patients with acute HF and 43% of patients with chronic HF have ischemic etiology, the relatively high use of nitrate may be attributed to related ischemic heart disease. However, limited data are available to support oral nitrate use in these patients. The efficacy of nitrate alone in treatment of ischemic HF was retrospectively investigated in a single-center study.⁴⁴ During the 5-year follow-up period, the use of chronic nitrates (N = 83) was associated with a higher incidence of fatal or nonfatal myocardial infarction or stroke. Despite some limitations, such as few patients, a lack of

tendency to match, and relatively few adverse events, this previous study showed that use of nitrate increased mortality. Farag et al.⁴⁵ conducted a systematic review of RCTs to assess whether use of hydrazine and nitrate alone or in combination could improve survival rates. Although combined use of these two drugs reduced the total mortality and mortality rates of cardiovascular disease compared with placebo, both types of mortality rates were significantly higher compared with those with angiotensin-converting enzyme inhibition. The effects of nitrate alone on mortality were tested in seven studies, and a two-fold increase in total mortality compared with placebo was found. However, the incidence of events was small (N=13), especially in the nitrate group, which was a reliable comparison. A strength of the present meta-analysis was that the number of patients was relatively high. However, our analysis showed that nitrate did not improve the daily activity level, submaximal exercise ability, and quality of life scores.

The effects of nitrate alone on the long-term prognosis of patients with HF with preserved ejection fraction using life-saving and disease-improved therapies are unclear. At present, the only trial on the use of nitrate was performed in patients with HF with preserved ejection fraction, and no beneficial effect on motor ability was shown in 6 weeks after nitrate treatment.³² Nevertheless, nitrates may have additional hemodynamic benefits for patients with HF with reduced ejection fraction who have ongoing symptoms, despite optimal management. Nitrate is used in combination with other vasodilators, such as enalapril, to help influence clinical outcomes by improving the nitrate–nitrite–nitric oxide pathway and reducing preload caused by venous vasodilation.

Our meta-analysis has some limitations follows. First, the analysis might have been compromised by extracting raw data

from the included studies. Second, the follow-up time of 14 studies (from 1–57 months) greatly varied, limiting the assessment of long-term clinical efficacy of nitrates in patients with HF. Third, the language might also have introduced prejudice. Specifically, only English was selected to exclude other qualified researchers. Fourth, only two studies for each of the different outcomes met the inclusion criteria. Therefore, controlling for any significant heterogeneity was difficult if it existed. Finally, this study included HF with preserved and reduced ejection fractions. Therefore, clinical and pathophysiological differences might have been a source of clinical heterogeneity.

Conclusions

Despite the limitations, this meta-analysis shows no improvement in the quality of life or submaximal exercise capacity in patients with HF who have nitrate treatment compared with patients with HF receiving control treatment. Additionally, nitrate does not affect all-cause mortality and the hospitalization risk in patients with HF. Further research is required on larger data sets and well-designed models to validate our results.

Acknowledgments

We are grateful to Professor Licheng Zhao (Guangzhou University of Chinese Medicine) for his inspiring guidance in this work. We also thank Miss Jingyi Xu for her critical revision of the article.

Author contributions

ZY and SX contributed to the conception or design of the work. WL, JL, YN, ZZ, TW, and JK contributed to acquisition, analysis, or interpretation of data for the work. QL and WL drafted the manuscript. LW and HL critically revised the manuscript. All authors gave final

approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This work was funded by the National Science Foundation of China (grant numbers: 8170151228, 81473621, and 817015128) and the National Key Research and Development Plan (No. 2018YFC1707401).

ORCID iD

Zhongqi Yang  <https://orcid.org/0000-0003-3582-2672>

References

1. Cao B, Bray F, Beltran-Sanchez H, et al. Benchmarking life expectancy and cancer mortality: global comparison with cardiovascular disease 1981-2010. *BMJ* 2017; 357: j2765.
2. Bansilal S, Castellano JM and Fuster V. Global burden of CVD: focus on secondary prevention of cardiovascular disease. *Int J Cardiol* 2015; 201: S1-S17.
3. Hameed SS, Rawal I, Soni D, et al. Technology for diagnosis, treatment, and prevention of cardiometabolic disease in India. *Prog Cardiovasc Dis* 2016; 58: 620-629.
4. Anchique Santos CV, Lopez-Jimenez F, Benaim B, et al. Cardiac rehabilitation in Latin America. *Prog Cardiovasc Dis* 2014; 57: 268-275.
5. Tendera M. Epidemiology, treatment, and guidelines for the treatment of heart failure in Europe. *Eur Heart J Suppl* 2005; 7: J5-J9.
6. McMurray JJV and Stewart S. The burden of heart failure. *Eur Heart J Suppl* 2003; 5: 3-13.
7. Lane DA, Chong AY and Lip GY. Psychological interventions for depression in heart failure. *Cochrane Database Syst Rev* 2005; 5: CD003329.
8. Stewart S, MacIntyre K, Capewell S, et al. Heart failure and the aging population: an increasing burden in the 21st century? *Heart* 2003; 89: 49-53.
9. Cohn JN. Nitrates for congestive heart failure. *Am J Cardiol* 1985; 56: 19A-23A.
10. Yusuf S, Pitt B, Davis CE, et al. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991; 325: 293-302.
11. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997; 336: 525-533.
12. Dupuis J, Lalonde G, Lebeau R, et al. Sustained beneficial effect of a seventy-two hour intravenous infusion of nitroglycerin in patients with severe chronic congestive heart failure. *Am Heart J* 1990; 120: 625-637.
13. Dupuis J, Lalonde G, Bichet D, et al. Captopril does not prevent nitroglycerin tolerance in heart failure. *Can J Cardiol* 1990; 6: 281-286.
14. Mehra A, Shotan A, Ostrzega E, et al. Potentiation of isosorbide dinitrate effects with N-acetylcysteine in patients with chronic heart failure. *Circulation* 1994; 89: 2595-2600.
15. Zakeri R, Levine JA, Koepp GA, et al. Nitrate's effect on activity tolerance in heart failure with preserved ejection fraction trial: rationale and design. *Circ Heart Fail* 2015; 8: 221-228.
16. Schwartzberg S, Redfield MM, From AM, et al. Effects of vasodilation in heart failure with preserved or reduced ejection fraction implications of distinct pathophysiologies on response to therapy. *J Am Coll Cardiol* 2012; 59: 442-451.
17. Von Lueder TG and Atar D. Comorbidities and polypharmacy. *Heart Fail Clin* 2014; 10: 367-372.
18. Hare JM. Nitroso-redox balance in the cardiovascular system. *N Engl J Med* 2004; 351: 2112-2114.
19. Macdonald P, Schyvens C and Winlaw D. The role of nitric oxide in heart failure. Potential for pharmacological intervention. *Drugs Aging* 1996; 8: 452-458.

20. Dixon LJ, Morgan DR, Hughes SM, et al. Functional consequences of endothelial nitric oxide synthase uncoupling in congestive cardiac failure. *Circulation* 2003; 107: 1725–1728.
21. Cole RT, Gupta D and Butler J. Current perspectives on hydralazine and nitrate therapies in heart failure. *Heart Fail Clin* 2014; 10: 565–576.
22. Knowles HJ, Tian YM, Mole DR, et al. Novel mechanism of action for hydralazine: induction of hypoxia-inducible factor-1 α , vascular endothelial growth factor, and angiogenesis by inhibition of prolyl hydroxylases. *Circ Res* 2004; 95: 162–169.
23. Munzel T, Kurz S, Rajagopalan S, et al. Hydralazine prevents nitroglycerin tolerance by inhibiting activation of a membrane-bound NADH oxidase. A new action for an old drug. *J Clin Invest* 1996; 98: 1465–1470.
24. Franciosa JA, Nordstrom LA and Cohn JN. Nitrate therapy for congestive heart failure. *JAMA* 1978; 240: 443–446.
25. Leier CV, Huss P, Magorien RD, et al. Improved exercise capacity and differing arterial and venous tolerance during chronic isosorbide dinitrate therapy for congestive heart failure. *Circulation* 1983; 67: 817–822.
26. Unverferth DV, Mehegan JP, Magorien RD, et al. Regression of myocardial cellular hypertrophy with vasodilator therapy in chronic congestive heart failure associated with idiopathic dilated cardiomyopathy. *Am J Cardiol* 1983; 51: 1392–1398.
27. Elkayam U, Amin J, Mehra A, et al. A prospective, randomized, double-blind, crossover study to compare the efficacy and safety of chronic nifedipine therapy with that of isosorbide dinitrate and their combination in the treatment of chronic congestive heart failure. *Circulation* 1990; 82: 1954–1961.
28. Elkayam U, Johnson JV, Shotan A, et al. Double-blind, placebo-controlled study to evaluate the effect of organic nitrates in patients with chronic heart failure treated with angiotensin-converting enzyme inhibition. *Circulation* 1999; 99: 2652–2657.
29. Lewis BS, Rabinowitz B, Schlesinger Z, et al. Effect of isosorbide-5-mononitrate on exercise performance and clinical status in patients with congestive heart failure. Results of the Nitrates in Congestive Heart Failure (NICE) Study. *Cardiology* 1999; 91: 1–7.
30. Tingberg E, Roijer A, Thilen U, et al. Randomized, double-blind, placebo-controlled long-term study of isosorbide-5-mononitrate therapy in patients with left ventricular dysfunction after acute myocardial infarction. *Am Heart J* 2003; 145: E1.
31. Herrero-Puente P, Jacob J, Martin-Sanchez FJ, et al. Influence of Intravenous nitrate treatment on early mortality among patients with acute heart failure. NITRO-EAHFE Study. *Rev Esp Cardiol (Engl Ed)* 2015; 68: 959–967.
32. Redfield MM, Anstrom KJ, Levine JA, et al. Isosorbide mononitrate in heart failure with preserved ejection fraction. *N Engl J Med* 2015; 373: 2314–2324.
33. Ho EC, Parker JD, Austin PC, et al. Impact of nitrate use on survival in acute heart failure: a propensity-matched analysis. *J Am Heart Assoc* 2016; 5: e002531.
34. Sliwa K, Damasceno A, Davison BA, et al. Bi treatment with hydralazine/nitrates vs. placebo in Africans admitted with acute HEart Failure (BA-HEF). *Eur J Heart Fail* 2016; 18: 1248–1258.
35. Lim SL, Benson L, Dahlstrom U, et al. Association between use of long-acting nitrates and outcomes in heart failure with preserved ejection fraction. *Circ Heart Fail* 2017; 10: e003534.
36. Ural D, Kandemir AS, Karauzum K, et al. Effect of oral nitrates on all-cause mortality and hospitalization in heart failure patients with reduced ejection fraction: a propensity-matched analysis. *J Card Fail* 2017; 23: 286–292.
37. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; 151: 264–269, w64.
38. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343: d5928.
39. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in

- meta-analyses. *Eur J Epidemiol* 2010; 25: 603–605.
40. Tsujimoto T and Kajio H. Use of nitrates and risk of cardiovascular events in patients with heart failure with preserved ejection fraction. *Mayo Clin Proc* 2019; 94: 1210–1220.
 41. Egger M and Smith GD. Meta-Analysis. Potentials and promise. *BMJ* 1997; 315: 1371–1374.
 42. Zwahlen M, Renahan A and Egger M. Meta-analysis in medical research: potentials and limitations. *Urol Oncol* 2008; 26: 320–329.
 43. Farag M, Shoib A and Gorog DA. Nitrates for the management of acute heart failure syndromes, A systematic review. *J Cardiovasc Pharmacol Ther* 2017; 22: 20–27.
 44. Maggioni AP, Anker SD, Dahlstrom U, et al. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2013; 15: 1173–1184.
 45. Farag M, Mabote T, Shoib A, et al. Hydralazine and nitrates alone or combined for the management of chronic heart failure: a systematic review. *Int J Cardiol* 2015; 196: 61–69.